1,195,066

PATENT SPECIFICATION

NO DRAWINGS

1,195,066

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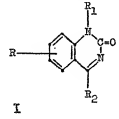
COMPLETE SPECIFICATION

Quinazolinones and Pharmaceutical Compositions thereof

We, SANDOZ LTD., of Lichtstrasse 35, Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to quinazolines and to their preparation.

The present invention provides compounds of the general formula I,



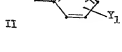
I

in which

R signifies a hydrogen, fluorine, bromine or chlorine atom;

R_1 signifies an alkyl radical of from 1 to 5 carbon atoms other than a tertiary alkyl radical in which the tertiary carbon atom is directly attached to the nitrogen atom of the quinazoline ring, or an allyl or propargyl radical; and

R_2 signifies a phenyl radical or a substituted phenyl radical of the general formula II,



II

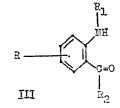
in which

Y signifies a fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, an alkoxy radical of 1 to 4 carbon atoms, or a trifluoromethyl radical; and

Y_1 signifies a hydrogen, fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, or an alkoxy radical of 1 to 4 carbon atoms.

The present invention further provides methods of preparing compounds of general formula I, characterised in that

a) a compound of general formula III,



III

in which R, R_1 and R_2 are as defined above, is reacted at a temperature of 140°C or higher with an alkyl (C_1—C_2) carbamate in the presence of a catalytic amount of a Lewis acid, or

b) a compound of general formula IV,

IV

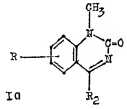
[*Price 5s. 0d.*]

in which R and R_2 are as defined above and M signifies an alkali metal atom, is reacted with a compound of general formula V,

$$R_1X \qquad V$$

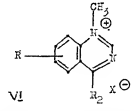
in which R_1 is as defined above and X signifies a bromine, chlorine or iodine atom, in the prcsence of an organic solvent which is inert under the reaction conditions, or

c) a compound of general formula Ia,



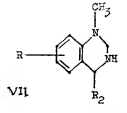
Ia

in which R and R_2 are as defined above, is obtained either by i) oxidising a compound of general formula VI,



VI

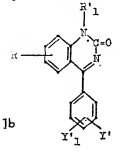
in which R_1, R_2 and X are as defined above, or by ii) oxidising a compound of general formula VII,



VII

in which R_1 and R_2 are as defined above, or

d) compound of general formula Ib,



Ib

in which

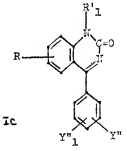
R is as defined above,

R'_1 signifies an alkyl radical of 1 to 5 carbon atoms other than a tertiary alkyl radical in which the tertiary carbon atom is directly attached to the nitrogen atom of the quinazolinone ring,

Y' signifies a fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, or a trifluoromethyl radical; and

Y'_1 signifies a hydrogen, fluorine, bromine or chlorine atom, a hydroxyl radical, or an alkyl radical of 1 to 4 carbon atoms, with the proviso that at least one of Y' and Y'_1 must signify a hydroxy radical,

is produced by hydrolysing a compound of general formula Ic,



Ic

in which

R and R'_1 are as defined above,

Y'' signifies a fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, an alkoxy radical of 1 to 4 carbon atoms, or a trifluoromethyl radical; and

Y''_1 signifies a hydrogen, fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, or an alkoxy radical of 1 to 4 carbon atoms, with the proviso that at least one of Y'' and Y''_1 must signify an alkoxy radical of 1 to 4 carbon atoms,

under acidic conditions suitable for the replacement of said alkoxy radical by a hydroxyl radical.

Method a) is conveniently carried out at an elevated temperature, preferably of from 160° to 200°C, the preferred Lewis acid being zinc chloride and the preferred carbamate being ethyl carbamate. If desired, the reaction may be carried out in an organic solvent which is inert under the reaction conditions, e.g. *o*-dichlorobenzene, but this is not necessary since an excess of the carbamate can be used for this purpose. Depending on the particular conditions employed, a suitable reaction time is from about 30 minutes to about 2 hours.

Method b) is conveniently carried out at a temperature of from room temperature (approximately 20°C) up to about 100°C., it

being preferred to commence the reaction at room temperature, e.g. for 1 to 4 hours, and then continue at reflux temperature. Suitable organic solvents which are inert under the reaction conditions include dimethylacetamide, diethylacetamide, dimethylformamide, dimethylsulfoxide and dioxane. Preferably, the compound of formula IV is a sodium of potassium salt, and the compound of formula V is preferably an iodide.

Method c) (i) is suitably effected in an organic solvent which is inert under the reaction conditions and at least partially water-miscible, e.g. dioxane or acetone, at, e.g. room temperature (approximately 20°C), using an aqueous solution of sodium permanganate or potassium permanganate as the oxidising agent.

The oxidation of a compound of formula VII in method c(ii) is suitably carried out in an organic solvent which is inert under the reaction conditions and at least partially water-miscible, e.g. dioxane or acetone, at, e.g. room temperature (approximately 20°C), using an aqueous solution of sodium permanganate or potassium permanganate as the oxidising agent.

Method d) is suitably carried out using aqueous hydrobromic acid or hydrobromic acid in acetic acid as the hydrolysing agent at a temperature of from 60° to 110°C, preferably at the reflux temperature.

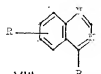
The compounds of formula I thus produced may readily be recovered and purified using conventional techniques.

The compounds of formula III used as starting materials in method a) are either known compounds or can be prepared from available materials by methods analogous to those described in the literature for the known compounds.

The compounds of formula IV used as starting materials in method b) may readily be obtained by treating the corresponding 1-unsubstituted quinazolinone in method known *per se* for the preparation of such alkali metal salts, e.g. with sodium hydride or an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide or potassium ethoxide. The reaction is suitably carried out at room temperature in an organic solvent which is inert under the reaction conditions, e.g. dimethylacetamide, diethylacetamide, dimethylformamide, dimethylsulfoxide or dioxane. Suitably the same solvent is used for the subsequent preparation of compounds of general formula I.

The 1-unsubstituted quinazolones themselves are either known or can be prepared from available starting materials in a manner analogous to that described in the literature (e.g. Japanese Patent No. 20865/65 published September 16, 1963) for known compounds.

The compounds of formula VI used as starting materials in method c) (i) may be obtained by reacting a compound of general formula VIII,



VIII

in which R and R_2 are as defined above, with a compound of general formula IX,

$$CH_3X \qquad IX$$

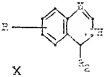
in which X is as defined above, at a temperature from about room temperature (approximately 20°C) to about 45°C, there being employed either an excess of the compound of formula IX or an organic solvent which is inert under the reaction conditions, e.g. chloroform or acetone, as reaction medium.

Preferably the reaction is commenced at room temperature, e.g. for 1 to 4 hours, and then continued at reflux temperature, using an excess of methyl iodide. When there is used a compound of formula IX, which is a gas at room temperature, it is of course desirable to use an organic solvent as reaction medium.

The resulting compound of formula VI may readily be recovered using conventional techniques.

Various compounds of formula VIII are themselves known and can be prepared by methods described in the literature (e.g. J. Chem. Soc., *1952*, 1927). Such others which are not specifically disclosed may be prepared from available materials in analogous manner.

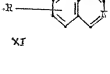
Alternatively the compounds of formula VIII may be prepared by oxidation of a compound of general formula X,



X

in which R and R_2 are as defined above. The oxidation is suitably carried out in an organic solvent which is inert under the reaction conditions and at least partially water-miscible, e.g. dioxane or acetone, at, e.g. room temperature (approximately 20°C), using an aqueous solution of sodium permanganate or potassium permanganate as oxidising agent.

The compounds of formula X may themselves be prepared by reacting a compound of general formula XI,



XI

in which R is as defined above, with a compound of general formula XII,

$$R_2P \qquad XII$$

in which P signifies a lithium atom or MgX', in which

X' signifies a chlorine or bromine atom.

The reaction is suitably carried out at room temperature (approximately 20°C) in an organic solvent which is inert under the reaction conditions, e.g. diethylether, and the P salt initially formed is decomposed in manner known *per se*, e.g. by treatment with water.

The compounds of formulae XI and XII ar either known or can be prepared from available starting materials by methods analogous to those described in the literature for the known compounds.

The compounds of formula VII used as starting materials in method c) (ii) may be obtained by reducing a compound of formula VI. The reduction is suitably carried out using a borohydride, e.g. sodium borohydride, as reducing agent, conveniently in the presence of an organic solvent which is inert under the reaction conditions, e.g. a lower alkanol such as methanol or ethanol, or a mixture of a lower alkanol with methylene chloride, chloroform or water. The reduction is desirably carried out at a temperature of from about room temperature (approximately 20°C) to about 80°C. The resulting compound of formula VII may be isolated and purified by conventional techniques. However, in general it has a tendency to be somewhat unstable and, therefore, if it is to be used to prepare a compound of formula Ia it is desirable to oxidise it as soon as possible.

The compounds of formula Ic used as starting materials for method d) may be prepared by method a) or b) or, additionally, when the 1-substituent is a methyl radical, by method c), using starting materials in which R_2 is alkoxy-substituted. It will be appreciated that compounds of formula Ib may also be prepared directly by methods a), b) and c) using starting materials which are hydroxy-substituted, but method d) is the preferred method.

The compounds of general formulae VI and VII are new compounds.

The compounds of general formula I possess pharmacological activity in animals. In particular, they have an anti-inflammatory effect.

The compounds of formula I may be used as pharmaceuticals on their own or in the form of appropriate medicinal preparations for administration, e.g. orally or parenterally. In order to produce suitable medicinal preparations the compounds may be worked up with organic or inorganic adjuvants which are physiologically inert.

Examples of such adjuvants are:

for tablets and dragées : lactose, starch, talcum, stearic acid;

for syrups : solutions of cane sugar, invert sugar and glucose;

for injectable solutions or suspensions : water, alcohols, glycerin and vegetable oils.

The preparations may further contain suitable preserving, stabilising and wetting agents, solubilizers, sweetening and colouring substances and flavourings.

The present invention thus further provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of general formula I in association with a physiologically acceptable carrier or diluent.

The compounds of general formula I may, for example, be used for oral administration in the form of a tablet having the following weight composition: 1 to 3% of binding material (e.g. tragacanth), 3 to 10% of starch, 2 to 10% of talcum, 0.25 to 1% of magnesium stearate, the required amount of active material, and filling material, e.g. lactose, to make up 100%.

For the above mentioned uses, the dosage administered will, of course, vary depending on the compounds used, the therapy desired and the mode of administration. However, in general, satisfactory results are obtained when the compounds are administered at a daily dosage of from about 0.5 mg to about 150 mg/kg of body weight, preferably given in divided doses 2 to 4 times a day or in retard form.

For most mammals the administration of from about 40 mg to about 400 mg of the compound per day provides satisfactory results, and dosage forms suitable for internal administration comprise from about 10 mg to about 200 mg of the compound in admixture with a solid or liquid pharmaceutical carrier or diluent.

A representative formulation is a tablet prepared by conventional tabletting techniques and containing the following ingredients:

Ingredient	Parts by Weight
Compound of formula I, e.g. 1-ethyl-4-phenyl-2(1H) quinazolinone	50
tragacanth	2
lactose	39.5
corn starch	5
talcum	3
magnesium stearate	0.5

EXAMPLE 1:
1-methyl-4-phenyl-2(1H)-quinazolinone.
[*via* method (c) i)]

a) Preparation of 1 - methyl - 4 - phenyl-quinazolinium iodide.

A solution of 2.0 g of 4-phenylquinazoline in 10 ml of methyl iodide is kept at room temperature (approximately 20°C) overnight and then refluxed for 8 hours. The resulting mixture is then cooled, and the crystalline material thus obtained is filtered off and washed with diethyl ether to obtain 1 - methyl-4 - phenyl - quinazolinium iodide, M.P. 200 210°C.

b) Preparation of 1 - methyl - 4 - phenyl-2(1H) - quinazolinone.

To a suspension of 5.7 g of 1 - methyl - 4-phenyl - quinazolinium iodide in 300 ml of purified dioxane is added slowly a solution of 4 g of potassium permanganate in 150 ml of water. The reaction mixture is maintained at room tmperature (approximately 20°C) for 15 minutes and then 10 ml of commercial dioxane and 25 ml of 1% aqueous solution of sodium thiosulfate are added to destroy the excess permanganate and reduce any iodine which is formed. The resulting mixture is then filtered, the filtrate concentrated to about 100 ml *in vacuo* and 80 ml of methylene chloride and 80 ml of water added thereto. The organic phase is separated, washed first with 50 ml of aqueous (2%) sodium carbonate solution and then with 40 ml of water and then dried over sodium sulfate and evaporated *in vacuo*. The residue is dissolved in 10 ml of ethyl acetate. To the resulting solution is added 8 ml of diethyl ether and the resulting crystalline material filtered off to obtain 1 - methyl-4 - phenyl - 2(1H) - quinazolinone, M.P. 142 —143°C.

EXAMPLE 2:
1-methyl-4-phenyl-2(1H)-quinazolinone
[*via* method (c) ii)]

a) Preparation of 1 - methyl - 4 - phenyl-1,2,3 - tetrahydroquinazoline.

To a solution of 18 g. of 1 - methyl - 4-phenyl - quinazolinium iodide in 500 ml of absolute ethanol and 250 ml of methylene chloride is added, in small portions and at room temperature (approximately 20°C), 6 g of sodium borohydride. After 45 minutes, 3 ml of acetic acid is added to destroy the excess sodium borohydride. The solvents are then evaporated off *in vacuo*, and the residue treated with 180 ml of methylene chloride and 10 ml of aqueous 5N sodium hydroxide solution. The organic phase is then separated, washed with 250 ml of water, dried over sodium sulfate and then evaporated to obtain 1 - methyl-4 - phenyl - 1,2,3,4 - tetrahydroquinazoline as an oil.

b) Preparation of 1 - methyl - 4 - phenyl-2(1H) - quinazolinone.

To a solution of 12 g of 1 - methyl - 4-phenyl - 1,2,3,4 - tetrahydroquinazoline in 500 ml of purified dioxane is slowly added a solution of 13.2 g of potassium permangate in 250 ml of water. After the addition is completed the reaction mixture is kept at room temperature (approximately 20°C) for 10 minutes and then 25 ml of commercial dioxane is added to destroy the excess permanganate The resulting mixture is then filtered, and the filtrate concentrated to about 100 ml *in vacuo*. To the resultant is added 120 ml of methylene chloride and 150 ml of water The organic phase is separated, washed first with 150 ml of aqueous (2%) sodium carbonate solution, then with 100 ml of water and then dried over sodium sulfate and evaporated *in vacuo*. The residue is dissolved in 30 ml of ethyl acetate. To the resulting solution is added 15 ml of diethyl ether, and the crystalline material thus obtained filtered off to obtain 1 - methyl - 4-phenyl - 2(1H) - quinazolinone, M.P. 142—143°C.

EXAMPLE 3:
1-methyl-4-phenyl-2(1H)-quinazolinone.
[*via* method (a)]

A mixture of 1.0 g of *o*-methylamino-benzophenone, 2.0 g of urethane and 20 mg of zinc chloride is heated for one and a quarter hours at 180—190°C on an oil bath. The resulting mixture is cooled to room temperature (approximately 20°C) and the resulting solid material treated with 100 ml of a 1:1 mixture of methylene chloride and water. The organic phase is separated, dried over anhydrous sodium sulfate, filtered and the solvent evaporated off. The residue is crystallized from ethyl acetate to obtain 1 - methyl - 4 - phenyl-2(1H) - quinazolinone, M.P. 141—143°C.

EXAMPLE 4:
1-ethyl-4-phenyl-2(1H)-quinazolinone.
[*via* method (b)]

To a solution of 2.2 g of 4 - phenyl - 2-(1H) - quinazolinone in 50 ml. of dimethyl-acetamide is added, at room temperature (approximately 20°C), 0.75 g of sodium hydride (50% in mineral oil). The resulting

mixture is stirred for 15 minutes at room temperature and then 4 ml of ethyl iodide is added. The mixture is stirred for an additional 30 minutes at room temperature and then heated at 60°C for 30 minutes to complete the reaction. The mixture is then evaporated *in vacuo* to remove most of the solvent, and the residue poured over 100 g of ice. The resulting solid material is filtered off, dissolved in 50 ml of methylene chloride and the resulting solution dried over sodium sulfate and the solvent then evaporated *in vacuo*. The resulting oily residue is crystallized from ethyl acetate to obtain 1 - ethyl - 4 - phenyl - 2-(1H) - quinazolinone, M.P. 183—185°C.

EXAMPLE 5:

6-chloro-1-methyl-4-phenyl-2(1H)-quinazolinone.

[*via* method (b)]

To a solution of 2.56 g of 6 - chloro - 4-phenyl- 2(1H) - quinazolinone in 100 ml of dimethylformamide is added, at room temperature (approximately 20°C), 0.75 g of sodium hydride (50% in mineral oil). The resulting mixture is stirred for 15 minutes at room temperature, and then 4 ml of methyl iodide is added. The mixture is then stirred at room temperature for an additional 30 minutes, then evaporated *in vacuo* to remove most of the solvent and then poured over 100 g of ice. The resulting solid material is filtered off and dissolved in 50 ml of methylene chloride. The resulting solution is dried over sodium sulfate and the solvent then evaporated *in vacuo*. The resulting oily residue is crystallized from ethyl acetate to obtain 6 - chloro-1 - methyl - 4 - phenyl - 2(1H) - quinazolinone, M.P. 223—224°C.

EXAMPLE 6:

1-methyl-4-(*p*-chlorophenyl)-2H-(1H)-quinazolinone.

[*via* method (c)ii)]

a) Preparation of 4 - (*p* - chlorophenyl)-quinazoline.

An ethereal solution of *p*-chlorophenyl lithium is prepared by reacting 0.96 g of *p*-bromo-chlorobenzene in 10 ml of absolute diethyl ether with 3.1 ml of a 1.6 molar solution of n-butyl lithium in hexane, at room temperature (approximately 20°C) for 30 minutes. To this solution is added a solution of 0.65 g of quinazoline in 10 ml of absolute diethyl ether and the resulting mixture is stirred for 10 minutes. The resulting lithium salt is decomposed by shaking the reaction mixture with 10 ml of water. The organic phase is then separated, dried over anhydrous sodium sulfate, filtered and the filtrate evaporated *in vacuo*. The residue is crystallized from ethyl acetate to obtain 4 - (*p* - chlorophenyl)-3,4 - dihydroquinazoline, M.P. 166—167°C.

To a solution of 5.0 g of 4 - (*p* - chlorophenyl) - 3,4 - dihydroquiazoline in 200 ml of dry dioxane is added, portionwise at room temperature, 60 ml of aqueous potassium permanganate solution (5.27 g of potassium permanganate in 100 ml of water). The excess permanganate is then destroyed by the dropwise addition of formic acid until the solution is colorless. The precipitated inorganic material is then filtered off and the filtrate evaporated *in vacuo*. The residue is treated with 100 ml of a 1:1 mixture of methylene chloride and water, the organic phase separated, dried over anhydrous sodium sulfate, filtered and the filtrate evaporated *in vacuo*. The residue is crystallized from diethyl ether to obtain 4 - (*p*-chlorophenyl) - quinazoline, M.P. 122—123°C.

b) Preparation of 1 - methyl - 4 - (*p*-chlorophenyl) - quinazolinium iodide.

A solution of 4,5 g of 4 - (*p* - chlorophenyl)-quinazoline in 55 ml of methyl iodide is kept at room temperature (approximately 20°C) overnight and then refluxed for 18 hours. The resulting mixture is then cooled, and the crystalline material thus obtained is filtered off and washed with diethyl ether to obtain 1 - methyl - 4 - (*p* - chlorophenyl) - quinazolinium iodide, M.P. 222—225°C.

c) Preparation of 1 - methyl - 4 - (*p*-chlorophenyl) - 1,2,3,4 - tetrahydro - quinazoline.

To a solution of 6.7 g of 1 - methyl - 4-(*p* - chlorophenyl) - quinazolinium iodide in 200 ml of absolute ethanol and 100 ml of methylene chloride is added, in small portions and at room temperature (approximately 20°C), 3.5 g of sodium borohydride. After 45 minutes 1.5 ml of acetic acid is added to destroy the excess sodium borohydride. The solvents are then evaporated off *in vacuo* and the residue treated with 100 ml of methylene chloride and 5 ml of aqueous 5N sodium hydroxide solution. The organic phase is then separated, washed with 250 ml of water, dried over sodium sulfate and then evaporated to obtain 1 - methyl - 4 - (*p* - chlorophenyl)-1,2,3,4 - tetrahydroquinazoline as an oil.

d) Preparation of 1 - methyl - 4 - (*p*-chlorophenyl) - 2(1H) - quinazolinone.

To a solution of 0.5 g of 1 - methyl - 4-(*p* - chlorophenyl) - 1,2,3,4 - tetrahydroquinazoline in 20 ml of purified dioxane is slowly added a solution of 0.625 g of potassium permanganate in 12 ml of water. After the addition is completed, the reaction mixture is kept at room temperature (approximately 20°C) for 10 minutes and then 5 ml of commercial dioxane is added to destroy the excess permanganate. The resulting mixture is then filtered, and the filtrate concentrated to about 10 ml *in vacuo*. The resulting product is poured over ice-water, the resulting mixture filtered and the residue washed with water to obtain 1 - methyl - 4 - (*p* - chlorophenyl)-2(1H) - quinazolinone, M.P. 195°C.

EXAMPLE 7:

[Further illustration of method (c) ii)]

Following the procedure of Example 6 b) and employing an equivalent amount of each of the quinazolines enumerated below in place of the 4 - (*p* - chlorophenyl) - quinazoline used therein there are obtained the respective products set forth below:

Quinazoline	Product
(1) 4-(*p*-methoxyphenyl) quinazoline	(1) 1-methyl-4-(*p*-methoxyphenyl)-quinazolinium iodide, m.p. 228—232°C. (after recrystallization from ethanol).
(2) 4-(2,6-dimethoxyphenyl)-quinazoline	(2) 1-methyl-4-(2,6-dimethoxyphenyl)-quinazolinium iodide, m.p. 198—202°C. (dec.) (after recrystallization from ethyl acetate).
(3) 4-(*m*-chlorophenyl)-quinazoline	(3) 1-methyl-4-(*m*-chlorophenyl)-quinazolinium iodide, m.p. 200—210°C.
(4) 4-(*m*-trifluoromethyl-phenyl)-quinazoline	(4) 1-methyl-4-(*m*-trifluoromethylphenyl)-quinazolinium iodide
(5) 4-(2,3-dimethylphenyl)-quinazoline	(5) 1-methyl-4-(2,3-dimethylphenyl)-quinazolinium iodide, m.p. 208—210°C.

Following the procedure of Example 6 c) and employing an equivalent amount of each of the products enumerated above in place of the 1 - methyl - 4 - (*p* - chlorophenyl)-quinazolinium iodide used in Example 6 c) there are obtained the respective tetrahydroquinazolines set forth below:

(1) 1 - methyl - 4 - (*p* - methoxyphenyl)-1,2,3,4 - tetrahydroquinazoline (oil).

(2) 1 - methyl - 4 - (2,6 - dimethoxyphenyl) - 1,2,3,4 - tetrahydroquinazoline, m.p. 157°C. (after crystallization from ethyl acetate).

(3) 1 - methyl - 4 - (*m* - chlorophenyl)-1,2,3,4 - tetrahydroquinazoline (oil).

(4) 1 - methyl - 4 - (*m* - trifluoromethylphenyl) - 1,2,3,4 - tetrahydroquinazoline (oil).

(5) 1 - methyl - 4 - (2,3 - dimethylphenyl)-1,2,3,4 - tetrahydroquinazoline (oil).

Following the procedure of Example 6 d) and employing an equivalent amount of each of the tetrahydroquinazolines enumerated above in place of the 1 - methyl - 4 - (*p*-chlorophenyl) - 1,2,3,4 - tetrahydroquinazoline used in Example 6 d) there are obtained the respective quinazolinones set forth below:

(1) 1 - methyl - 4 - (*p* - methoxyphenyl)-2(1H) - quinazolinone, m.p. 184°C. (after recrystallization from ethyl acetate).

(2) 1 - methyl - 4 - (2,6 - dimethoxyphenyl) - 2(1H) - quinazolinone, m.p. 166—167°C. (after recrystallization from ethyl acetate).

(3) 1 - methyl - 4 - (*m* - chlorophenyl)-2(1H) - quinazolinone, m.p. 95—96°C. (after purification by precipitation of the hydrochloric salt from acetone and subsequent liberation of the free base and crystallization thereof from diethyl ether-petroleum ether (1:1)).

(4) 1 - methyl - 4 - (*m* - trifluoromethylphenyl) - 2(1H) - quinazolinone, m.p. 165—167°C. (after recrystallization from ethyl acetate-diethyl ether (1:1)).

(5) 1 - methyl - 4 - (2,3 - dimethylphenyl)-2(1H) - quinazolinone, m.p. 186—188°C. (after recrystallization from ethyl acetate).

EXAMPLE 8:

[Further illustration of method (b)]

Following the procedure of Example 5 and employing an equivalent amount of 4 - phenyl-2(1H) - quinazolinone in place of 6 - chloro-4 - phenyl - 2(1H) - quinazolinone and each of the halide reactants enumerated below in place of methyl iodide there are obtained the respective products set forth below:

Halide Reactant	Product
(1) n-propyl iodide	1-n-butyl-4-phenyl-2(1H)-quinazolinone, m.p. 131°C.
(2) n-butyl bromide	1-n-butyl-4-phenyl-2(1H)-quinazolinone, m.p. 103—104°C. (after crystallization from ethyl acetate-diethyl ether (1:1)).
(3) n-amyl bromide	1-n-amyl-4-phenyl-2(1H)-quinazolinone, m.p. 121—122°C.
(4) allyl iodide	1-allyl-4-phenyl-2(1H)-quinazolinone, m.p. 159—160°C.
(5) propargyl iodide	1-propargyl-4-phenyl-2(1H)-quinazolinone, m.p. 181°C. (after crystallization from ethanol).

EXAMPLE 9:
6-chloro-1-methyl-4-(*o*-chlorophenyl)-2(1H)-quinazolinone.
[*via* method (b)]

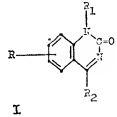
Following the procedure of Example 5 and employing an equivalent amount of 6 - chloro-4 - (*o* - chlorophenyl) - 2(1H) - quinazolinone, dimethylacetamide and sodium methoxide in place of 6 - chloro - 4 - phenyl - 2(1H)-quinazolinone, dimethylformamide and sodium hydride, respectively, there is obtained 6-chloro - 1 - methyl - 4 - (*o* - chlorophenyl)-2(1H) - quinazolinone, M.P. 191—194°C.

EXAMPLE 10:
1-methyl-4-(*p*-hydroxyphenyl)-2(1H)-quinazolinone.
[*via* method d)]

A mixture of 3 g of 4 - (*p* - methoxyphenyl) 1 - methyl - 2(1H) - quinazolinone and 20 ml of 48% aqueous hydrobromic acid is refluxed for 20 hours, concentrated *in vacuo* and then made alkaline (pH 9) with 2N aqueous ammonium hydroxide solution. The basic mixture is then extracted three times with 30 ml portions of ethyl acetate. The combined ethyl acetate extracts are then dried over anhydrous sodium sulfate, evaporated *in vacuo* and the residue then crystallized from ethyl acetate to obtain 1 - methyl - 4 - (*p* - hydroxyphenyl) - 2(1H) - quinazolinone, M.P. 291—293°C.

WHAT WE CLAIM IS:—

1. A method for the preparation of a compound of general formula I,

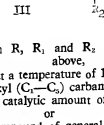


I

in which
R signifies a hydrogen, fluorine, bromine or chlorine atom;
R_1 signifies an alkyl radical of from 1 to 5 carbon atoms other than a tertiary alkyl radical in which the tertiary carbon atom is directly attached to the nitrogen atom of the quinazolinone ring, or an allyl or propargyl radical; and
R_2 signifies a phenyl radical or a substituted phenyl radical of the general formula II,

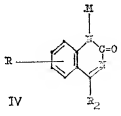
II

in which
Y signifies a fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, an alkoxy radical of 1 to 4 carbon atoms, or a trifluoromethyl ralical; and
Y_1 signifies a hydrogen, fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, or an alkoxy radical of 1 to 4 carbon atoms,
characterised in that
a) a compound of general formula III,



III

in which R, R_1 and R_2 are as defined above,
is reacted at a temperature of 140°C or higher with an alkyl (C_1—C_5) carbamate in the presence of a catalytic amount of a Lewis acid, or
(b) a compound of general formula IV,



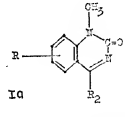
IV

in which R and R_2 are as defined above and M signifies an alkali metal atom,
is reacted with a compound of general formula V,

$$R_1X \qquad V$$

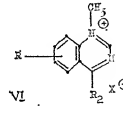
in which
R_1 is as defined above and
X signifies a bromine, chlorine or iodine atom,
in the presence of an organic solvent which is inert under the reaction conditions, or

c) a compound of general formula Ia,



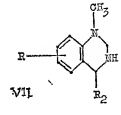
Ia

in which R and R_2 are as defined above, is obtained either by i) oxidising a compound of general formula VI,



VI

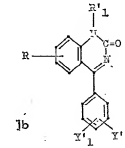
in which R_1, R_3 and X are as defined above,
or by ii) oxidising a compound of general formula VII,



VII

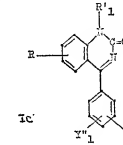
in which R_1 and R_2 are as defined above, or

d) a compound of general formula Ib,



Ib

in which
R is as defined above,
R'_1 signifies an alkyl radical of 1 to 5 carbon atoms other than a tertiary alkyl radical in which the tertiary carbon atom is directly attached to the nitrogen atom of the quinazolinone ring,
Y' signifies a fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, or a trifluoromethyl radical; and
Y'_1 signifies a hydrogen, fluorine, bromine or chlorine atom, a hydroxyl radical, or an alkyl radical of 1 to 4 carbon atoms, with the proviso that at least one of Y' and Y'_1 must signify a hydroxyl radical,
is produced by hydrolysing a compound of general formula Ic,



Ic

in which
R and R'_1 are as defined above,
Y'' signifies a fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, an alkoxy radical of 1 to 4 carbon atoms, or a trifluoromethyl radical; and
Y''_1 signifies a hydrogen, fluorine, bromine or chlorine atom, a hydroxyl radical, an alkyl radical of 1 to 4 carbon atoms, or an alkoxy radical of 1 to 4 carbon atoms, with the proviso that at least one of Y'' and Y''_1 must signify an alkoxy radical of 1 to 4 carbon atoms,
under acidic conditions suitable for the replacement of a lower alkoxy radical by a hydroxyl radical.

2. A method according to Claim 1, wherein

a compound of general formula III is treated with an excess of ethyl carbamate in the presence of zinc chloride at a temperature of from 160 to 200°C.

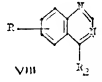
3. A method according to Claim 1, wherein a compound of formula IV is reacted with a compound of formula V at a temperature of from 20° to 100°C., the compound of formula IV being a sodium or potassium salt and the compound of formula V being an iodide.

4. A method according to Claim 1, wherein a compound of formula VI is oxidised in an organic solvent which is inert under the reaction conditions and at least partially water-miscible, at approximately 20°C using an aqueous solution of sodium or potassium permanganate as the oxidising agent.

5. A method according to Claim 1, wherein a compound of formula VII is oxidised in an organic solvent which is inert under the reaction conditions and at least partially water-miscible, at approximately 20°C using an aqueous solution of sodium or potassium permanganate as the oxidising agent.

6. A method according to Claim 1, wherein a compound of formula Ic is hydrolysed using aqueous hydrobromic acid or hydrobromic acid in acetic acid at a temperature of from 60° to 110°C.

7. A method according to Claim 1 or 4, wherein the compound of formula VI has been obtained by reacting a compound of general formula VIII,



VIII

in which R and R_2 are as defined in Claim 1,

with a compound of general formula IX,

$$CH_3X \qquad IX$$

in which X is as defined in Claim 1,

at a temperature of from about 20°C to about 45°C, there being employed either an excess of the compound of formula IX or an organic solvent which is inert under the reaction conditions as reaction medium.

8. A method according to Claim 1 or 5, wherein the compound of formula VII has been obtained by reducing a compound of formula VI.

9. A method according to Claim 8, wherein the reduction of the compound of formula VI is carried out using sodium borohydride at a temperature of from approximately 20°C to about 80°C in the presence of an inorganic solvent which is inert under the reaction conditions.

10. A method according to Claim 1 substantially as described in any one of the foregoing Examples.

11. Compounds of general formula I, as defined in Claim 1, whenever obtained by a method claimed in any one of Claims 1 to 10.

12. Compounds of general formula I, as defined in Claim 1.

13. 1 - methyl - 4 - phenyl - 2(1H) - quinazolinone.

14. 1 - ethyl - 4 - phenyl - 2(1H) - quinazolinone.

15. 6 - chloro - 1 - methyl - (4 - phenyl-2(1H) - quinazolinone.

16. 1 - methyl - 4 - (*p* - chlorophenyl)-2(1H) - quinazolinone.

17. 1 - methyl - 4 - (*p* - methoxyphenyl)-2(1H) - quinazolinone.

18. 1 - methyl - 4 - (2,6 - dimethoxyphenyl)-2(1H) - quinazolinone.

19. 1 - methyl - 4 - (*m* - chlorophenyl)-2(1H) - quinazolinone.

20. 1 - methyl - 4 - (*m* - trifluoromethylphenyl) - 2(1H) - quinazolinone.

21. 1 - methyl - 4 - (2,3 - dimethylphenyl)-2(1H) - quinazolinone.

22. 1 - n - propyl - 4 - phenyl - 2(1H)-quinazolinone.

23. 1 - n - butyl - 4 - phenyl - 2(1H)-quinazolinone.

24. 1 - n - amyl - 4 - phenyl - 2(1H)-quinazolinone.

25. 1 - allyl - 4 - phenyl - 2(1H) - quinazolinone.

26. 1 - propargyl - 4 - phenyl - 2(1H)-quinazolinone.

27. 6 - chloro - 1 - methyl - 4 - (*o* - chlorophenyl) - 2(1H) - quinazolinone.

28. 1 - methyl - 4 - (*p* - hydroxyphenyl)-2(1H) - quinazolinone.

29. Compounds of general formula VI, as defined in Claim 1, whenever obtained by a process specified in Claim 7.

30. Compounds of general formula VII, as defined in Claim 1, whenever obtained by a process specified in Claim 8 or 9

31. A pharmaceutical composition comprising a therapeutically effective amount of a compound claimed in any one of Claims 11 to 28 in association with a physiologically acceptable carrier or diluent.

32. A pharmaceutical composition according to Claim 31, substantially as hereinbefore described.

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